Microgravity-Induced Physiological Fluid Redistribution: Computational Analysis to Assess Influence of Physiological Parameters

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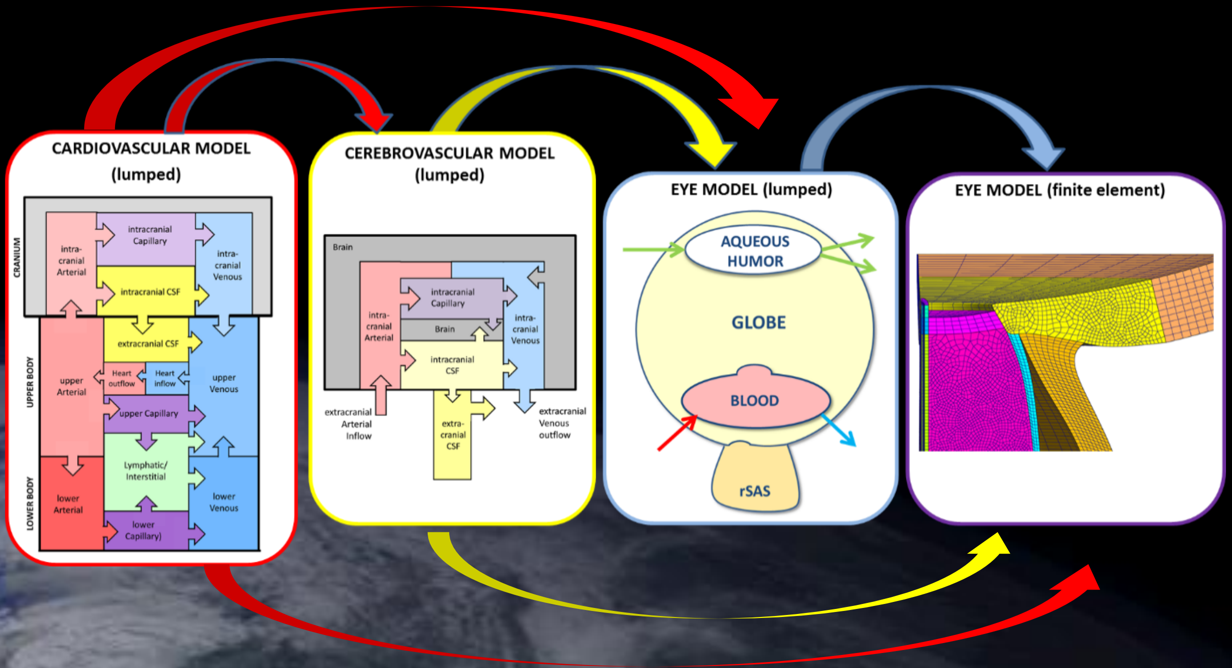
VIIP Modeling: Structured Approach

The suite of lumped parameter models should have the following capabilities:

- Bridge the gap between whole-body fluid shift in µg and biomechanical response of ocular tissues
- Identify parameters that have the most effect on *IOP* and *ICP* in µg
- Provide a platform to explore the physiological envelope and find patterns of behavior



Results Robustness

- Best practices with computer modeling includes establishing the robustness of the model
  – How well understood are the sensitivities of the model results to the variables and parameters of the model?

- Intent is to provide an understanding of the sensitivity of the real-world system to potential changes in the variables and parameters of the system
  – Assuming the modeled system behaves like the real-world system, this information improves model application.

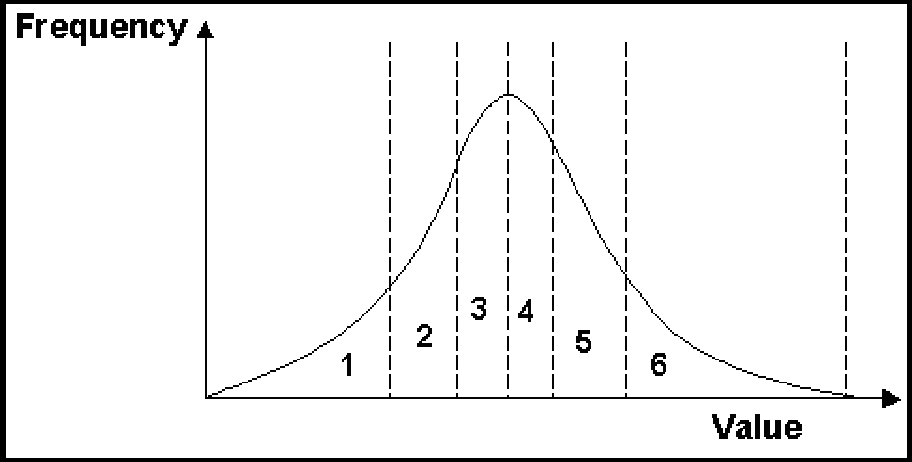
Sensitivity Analysis Methodology

- Saltelli: “Sensitivity Analysis is the study of how variation in the output of a model can be apportioned, qualitatively or <u>quantitatively</u>, to different sources of variation (input) and how the given model depends upon the information fed into it.”

- Partial Rank Correlation Coefficient (PRCC) Analysis
  – Provides a measure of the linear relationships between two variables (one input parameter and one output parameter) when all linear effects of other variables are removed after rank transformation.
  – Rank Transformation: transforms non-linear monotonic relations to linear.

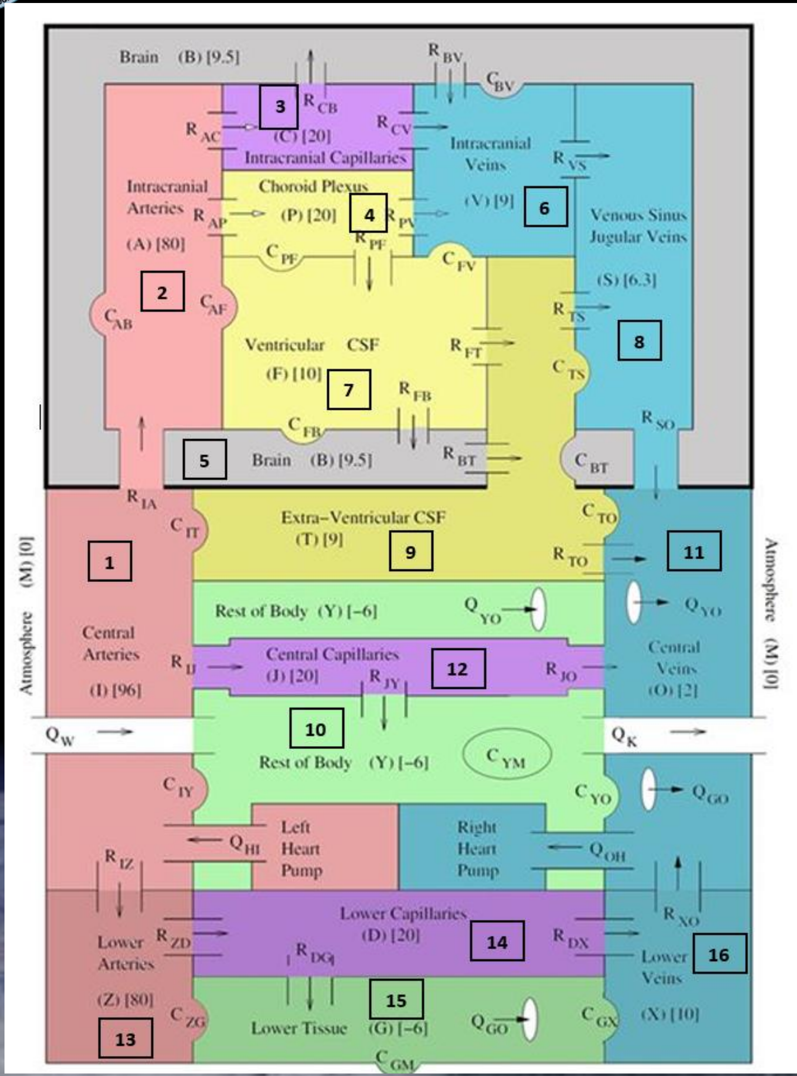
Latin Hypercube Sampling

- Latin Hypercube Sampling (LHS)
  - Sampling method without replacement
  - Improved sampling of distribution “tails”
  - Can achieve statistical convergence in fewer samples than standard Monte Carlo sampling



CVS Model:

Lakin et al: 16-compartment model



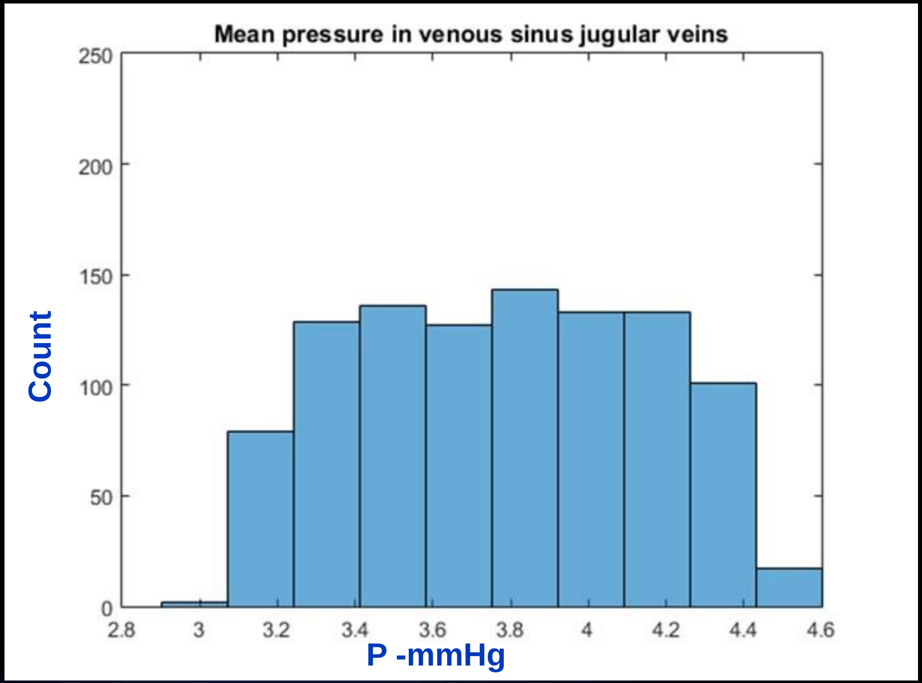
- Lumped (0-D) unsteady model
  - 16 Compartments
    - 13 blood, 3 CSF
  - Includes brain compartment
- Arteries, capillaries, veins are all represented in 3 locations
  - cranial, upper, lower

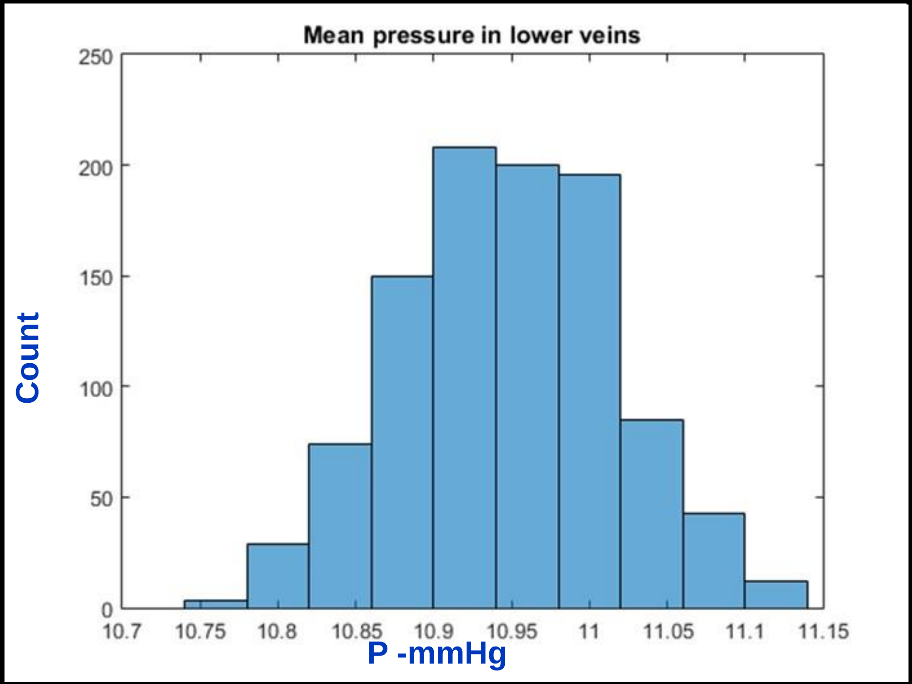
CVS Sensitivity Analysis

- 42 physiological parameters describe compartments
  - Supine steady state parameters
  - Mean pressure per compartment
  - Mean volumetric flow rates
  - Mean Distensability or Compliance
- Sensitivity Study
  - Range set at +/-10% assuming a uniform distribution
  - Model trained at 5000 ml/min, simulation at 6900 ml/min

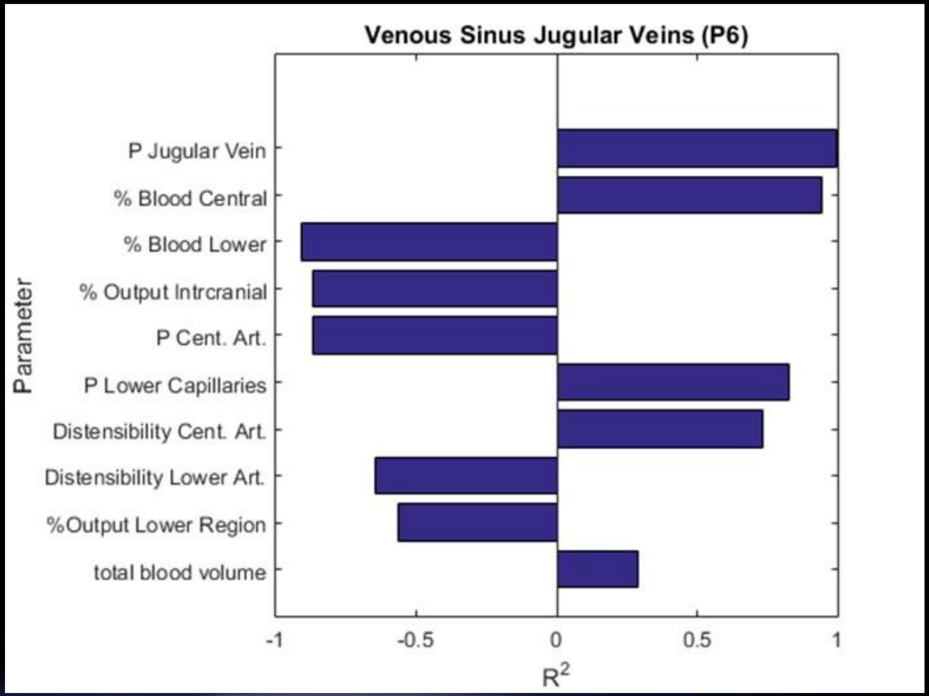
- Note: Pressures in mmHg, flows in ml/min

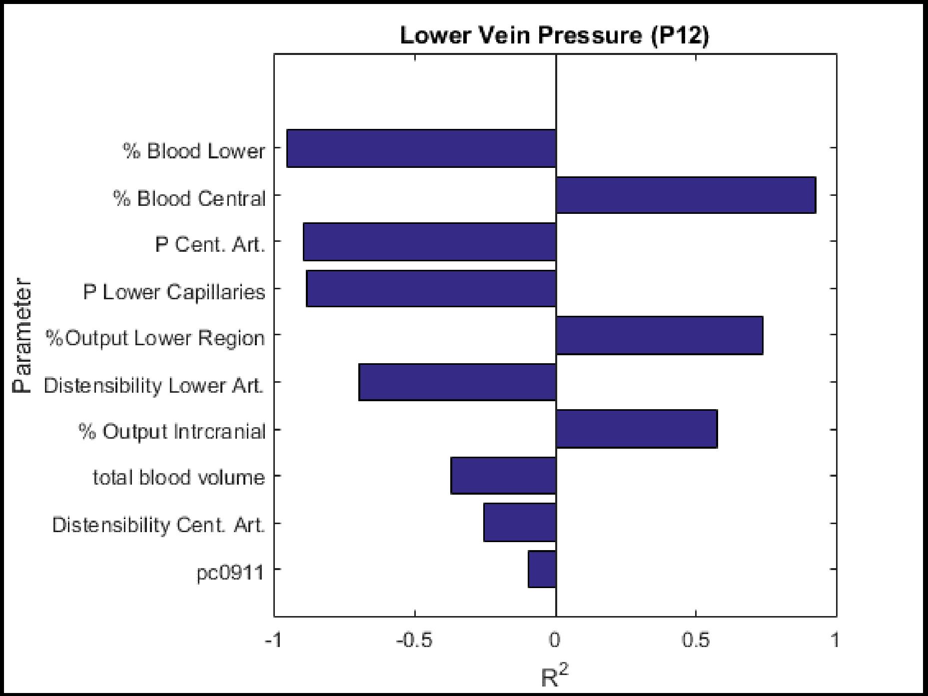
Output Uncertainty



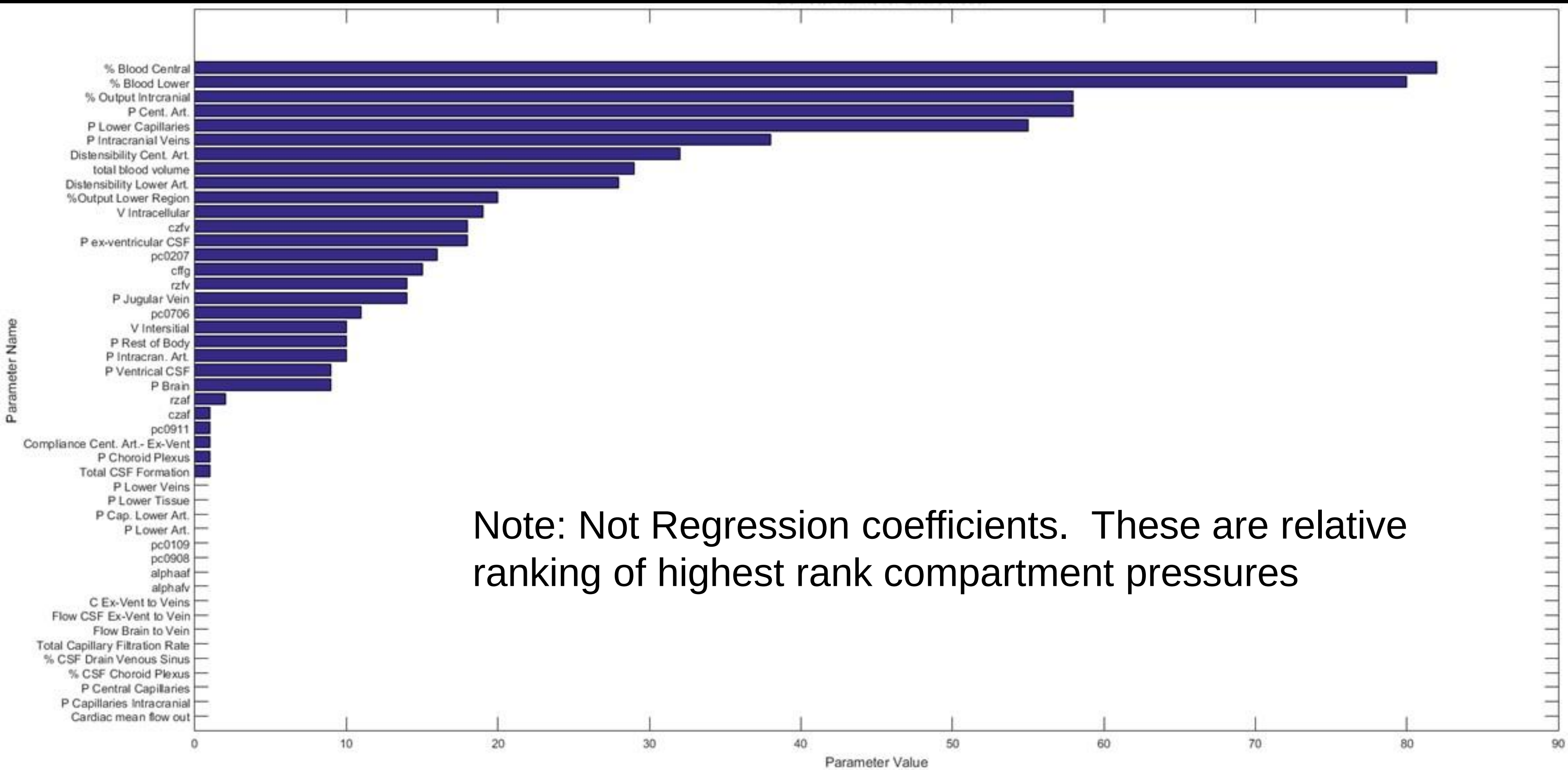


CVS - Sensitivity Analysis Results





Estimated Total Sensitivity of Model

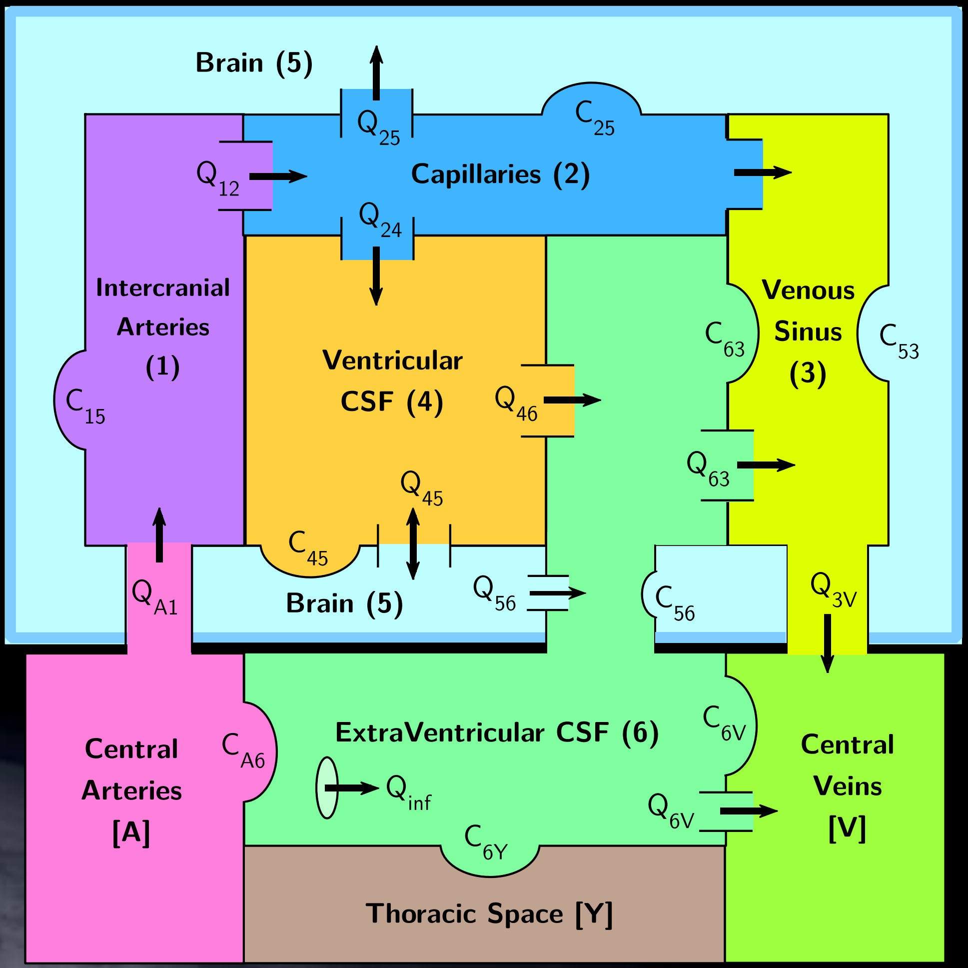


Note: Not Regression coefficients. These are relative ranking of highest rank compartment pressures

Reformulated CNS model

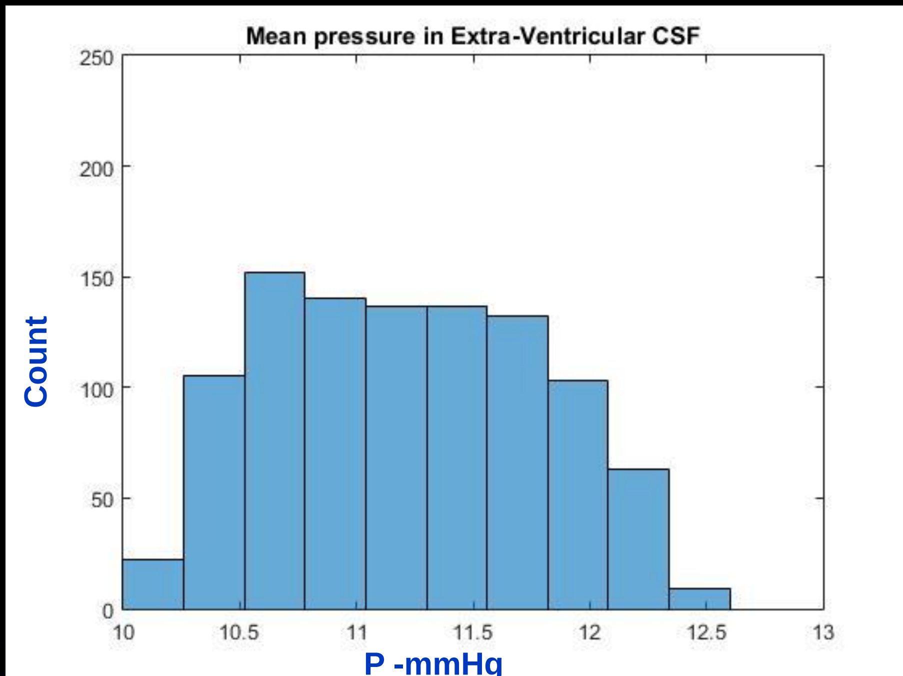
- Time-dependent model composed of 6 fluid compartments
  - 3 vascular:
  - 2 cerebrospinal fluid
  - 1 Brain
- Cranium and whole-body interaction provided by extracranial nodes
  - Central Arteries [A]
  - Central Veins [V]
  - Thoracic Space [Y]

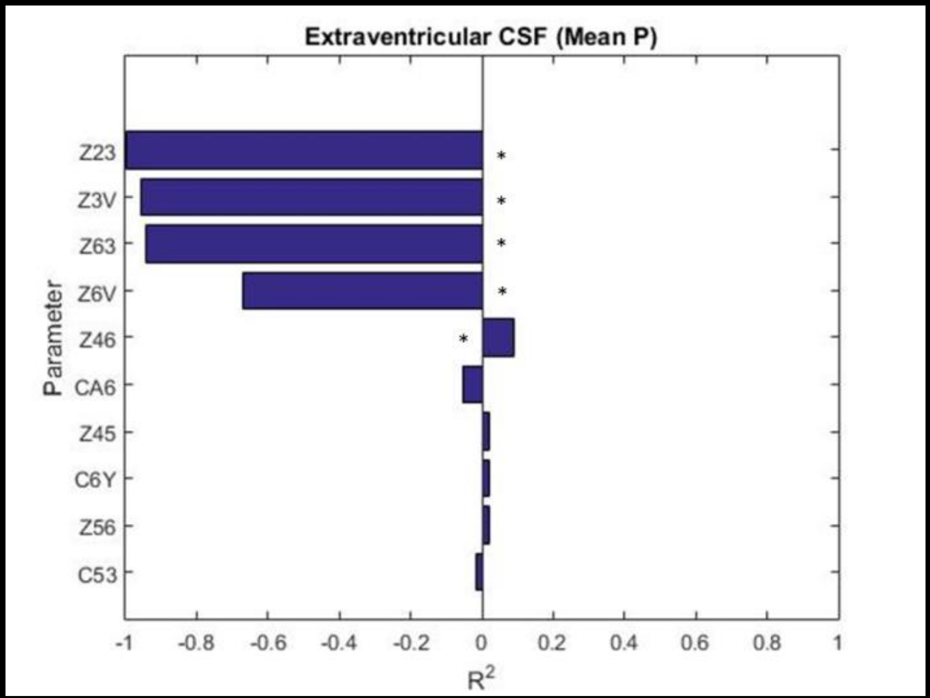
Q = Flowrates between compartments (ml/min)
C = Compartment compliance (ml / mmHg)
Z = Fluidity (1/R) between compartments (ml/ min*mmHg)



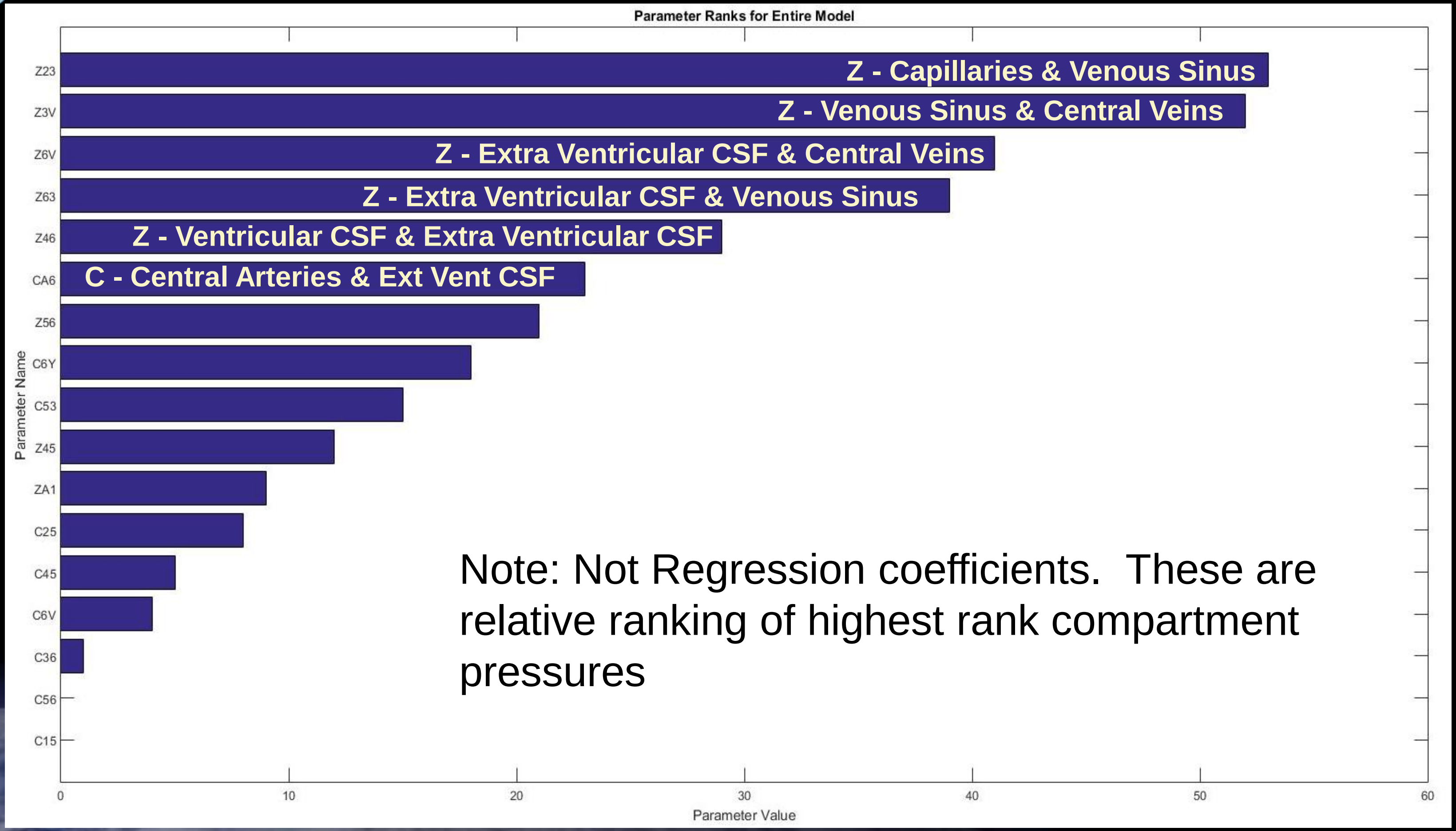
- Stevens et al. (2005)

Uncertainty and Sensitivity





CNS: Total Sensitivity



Findings: Model dominated by fluidity estimates. Venous compartment performance is particularly dependent on predefined percentage of cardiac output, much like CVS model.

Conclusions

- Parameter sensitivity analysis identified parameters of strongest influence, where special consideration should be applied
  - CVS model
    - Mean arterial flow distribution appears to be the major performance influence
      - Implies special consideration should be taken in specifying these values accurately to train the model to meet model performance goals
      - Performance will deviate more the further the application is from the training set point specified by these parameters
  - CNS model
    - Venous fluidity values have the greatest influence on all compartment pressures
      - Elimination of one compartment elevates sensitivity to venous pathway parameters
      - Illustrates model compartments may require further development; add Venous collapse

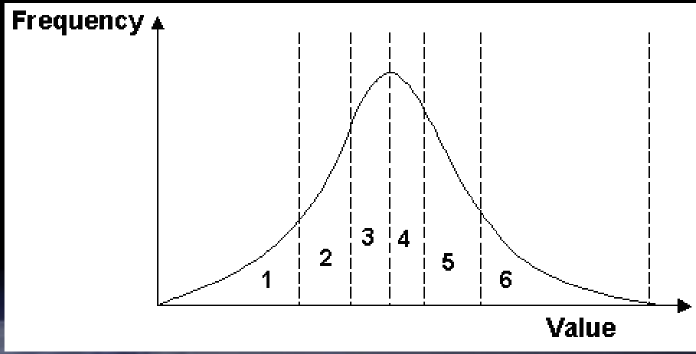
Future Efforts

- Technique extensible beyond just sensitivity
  - Provides substantial utility in predicting the population performance variability, per model outputs, than more traditional one-parameter at a time studies
  - Supports validation, experimental design and scenario analysis efforts
- Further efforts underway to assess model robustness in acute situations and chronic microgravity exposure

Backup Slides

Sampling and Correlation Coefficients

- Latin Hypercube Sampling (LHS)
  - Inputs: range, distribution type
  - Output: matrix of sample parameters



- Partial Rank Correlation Coefficients (PRCC)
  - Input: LHS matrix
  - Outputs: Correlation (-1 to 1) & p-value matrices

Size of Correlation	Interpretation
.00-.19	very weak
.20-.39	weak
.40-.59	moderate
.60-.79	strong
.80-1.0	very strong

42 Physiological Parameters

#	Name	Description	Value	Range
1	pf0113	%Output Lower Region	0.25	0.25-0.35
2	Qm07	Total CSF formation	0.4	0.35-0.40
3	QmH01	Cardiac mean flow out	6900	6500-7200
4	vblood	Total blood volume	5600	5000-5600
5	Pm(1)	Mean pressure in central arteries	96	5%
6	Pm(2)	Mean pressure in intracranial arteries	80	5%
7	Pm(3)	Mean pressure in intracranial capillaries	20	5%
8	Pm(4)	Mean pressure in choroid plexus	20	10%
9	Pm(5)	Mean pressure in brain	9.5	2%
10	Pm(6)	Mean pressure in intracranial veins	9	10%
11	Pm(7)	Mean pressure in ventricular CSF	10	2%
12	Pm(8)	Mean pressure in venous sinus /jugular veins	6.3	10%
13	Pm(9)	Mean pressure in extra-ventricular CSF	9	2%
14	Pm(10)	Mean pressure in rest of the body	-6	10%
15	Pm(11)	Mean pressure in lower capillaries	2	10%
16	Pm(12)	Mean pressure in central capillaries	20	10%
17	pf0102	% cardiac output: central arteries/intracranial arteries	0.15	10%
18	pf0407	% CSF formation from choroid plexus	0.7	10%
19	pf0908	% CSF drained into venous sinus	0.8	10%
20	Qm0307	Total capillary filtration	2	10%
21	Qm0506	Mean flow across the blood-brain barrier	0.001	10%
22	Qm0705	Mean flow across the CSF-brain barrier	0.044	10%
23	d(1)	Distensibility of the central arteries	0.00341196	10%
24	pvcentral	% systemic blood, central region	0.53	10%
25	cm0109	Compliance central arteries/extra-ventricular CSF	0.00571427	10%
26	cm0911	Compliance extra-ventricular CSF / central veins	0.200936	10%
27	vinterstitial	Interstitial fluid volume	12000	10%
28	vintracellular	Intracellular fluid volume	26000	10%
29	d(13)	Distensibility of the lower arteries	0.00169456	10%
30	pvlower	% systemic blood, lower region	0.4	10%

42 Physiological Parameters Part 2

31	pc0706	Percentage of the simplified 4-compartment model allocated to compliance across ventricle CSF and intracranial veins	0.164	10%
32	czfv	C coefficient used in four compartment model CSF/venous blood compliance equation (Lakin eqn 67), from eqn 68	6.5333	10%
33	rzfv	r coefficient used in four compartment model CSF/venous blood compliance equation (Lakin eqn 67), from eqn 68	0.633431	10%
34	alphafv	alpha coefficient used in four compartment model CSF/venous blood compliance equation (Lakin eqn 67), from eqn 68	0.604229	10%
35	alphaaf	alpha coefficient used in four compartment model arterial/ CSF compliance equation (Lakin eqn 67), from eqn 69	0.869393	10%
36	cffg	Four-compartment model constant compliance between CSF and rest of the body	0.13333	10%
37	pc0908	Percentage of the simplified 4-compartment model allocated to compliance across extra-ventricular CSF and venous sinus jugular veins	0.622	10%
38	pc0911	Percentage of the simplified 4-compartment model allocated to compliance across extra-ventricular CSF and central veins	0.214	10%
39	pc0207	Percentage of the simplified 4-compartment model allocated to compliance across intracranial arteries and ventricle CSF	0.786	10%
40	pc0109	Percentage of the simplified 4-compartment model allocated to compliance across central arteries and extra-ventricular CSF	0.214	10%
41	rzaf	r coefficient used in four compartment model arterial/ CSF compliance equation (Lakin eqn 67), from eqn 69	0.817102	10%
42	czaf	C coefficient used in four compartment model arterial/ CSF compliance equation (Lakin eqn 67), from eqn 69	1.82745	10%

Pressure Dependent Compliance, CSF

$$C^4 = C^o * e^{-r|P|^{\alpha}}$$

Compliance, General

$$C = \frac{dV}{dP} = D * V$$

Fluidity

$$Z = \frac{\bar{Q}}{\overline{P_{out}} - \overline{P_{in}}}$$

Input Data – Derived From Stevens et al

#	Name	Description	Value	Units	Range
1	C15	Compliance between Intercranial Arteries & Brain	0.0209523	mL / mmHg	10%
2	C25	Compliance between Capillaries & Brain	0.688845	mL / mmHg	10%
3	C53	Compliance between Brain & Venous Sinus	0.044444	mL / mmHg	10%
4	C36	Compliance between Venous Sinus & Extra Ventricular	1.27626	mL / mmHg	10%
5	C45	Compliance between Ventricular CSF & Brain	0.036255	mL / mmHg	10%
6	C56	Compliance between Brain & Extra Ventricular	0.137057	mL / mmHg	10%
7	CA6	Compliance between Central Arteries & Extra Ventricular	0.00571427	mL / mmHg	10%
8	C6V	Compliance between Extra Ventricular CSF & Central Veins	0.200936	mL / mmHg	10%
9	C6Y	Compliance between Extra Ventricular CSF & Thorasic Space	0.088889	mL / mmHg	10%
10	ZA1	Fluidity between the Central Arteries & Intercranial Arteries	103.5	mL/(min mmHG)	10%
11	Z23	Fluidity between the Capillaries & Venous Sinus	38.57	mL/(min mmHG)	10%
12	Z63	Fluidity between the Extra Ventricular CSF & Venous Sinus	0.1009	mL/(min mmHG)	10%
13	Z3V	Fluidity between the Venous Sinus & Central Veins	427.64	mL/(min mmHG)	10%
14	Z45	Fluidity between the Ventricular CSF & Brain	66	mL/(min mmHG)	10%
15	Z46	Fluidity between the Ventricular CSF & Extra Ventricular CSF	1.65	mL/(min mmHG)	10%
16	Z56	Fluidity between the Brain & Extra Ventricular CSF	0.642	mL/(min mmHG)	10%
17	Z6V	Fluidity between the Extra Ventricular CSF & Central Veins	0.0191	mL/(min mmHG)	10%

Statistical Convergence Test

- Number of LHS trials
  - Calculated change in standard deviation of central venous pressure for every 100 trials (100 vs. 200, 200 vs. 300…)
  - Converges below 0.002 after 1000 LHS trials